Applicants submit that no new matter is added by the foregoing amendments to the specification. Accordingly, entry of this amendment is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification by the amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning at page 5, line 28, has been amended as follows:

FIG. 10 shows an alignment of the amino acid sequence of human β-secretase ("Human Imapain.seq,") (SEQ ID NO: 2) compared to various mouse constructs (SEQ ID NOS:65 and 105-108).[, with the lowest construct in each row("pBS/mImpain H#3 cons") representing a consensus mouse sequence: SEQ ID NO: 65.]

The paragraph at page 6, lines 18 has been amended as follows:

FIG. 19 shows a schematic of an APP substrate fragment (SEQ ID NOS:103 and104), and it's use in conjunction with antibodies SW192 and 8E-192 in the assay.

The paragraph at page 6, lines 20 has been amended as follows:

FIG. 20 shows a schematic of [a schematic of a second] an APP substrate fragment (SEQ ID NOS:103 and104), and it's use in conjunction with antibodies SW192 and 8E-192 in the assay.

The following paragraphs have been added at page 8, lines 13, after the paragraphs added previously in the preliminary amendment mailed July 28, 2000.

SEQ ID NO:103 is the β-secretase cleavage sites in the wild-type APP sequence.

SEQ ID NO:104 is the β-secretase cleavage sites in the Swedish APP sequence.

SEQ ID NOS:105-109 are mouse constructs in alignment to the human β-secretase containing portions of β-secretase of Figure 10.

The paragraph at page 8, line 11 has been deleted and replaced with the following paragraph.

SEQ ID NO: 73 is P4-P4'staD→V. [(KTEEISEVN[sta]VAEF).]

The paragraph beginning at page 24, line 8, has been amended as follows:

The full-length open reading frame (ORF) of human β-secretase is described above, and its sequence is shown in FIG. 2A as SEQ ID NO: 2. However, as mentioned above, a further discovery of the present invention indicates that the predominant form of the active, naturally occurring molecule is truncated at the N-terminus by about 45 amino acids. That is, the [purified] protein purified from natural sources was N-terminal sequenced according to methods known in the art (Argo Bioanalytica, Morris Plains, NJ[,]). The N-terminus yielded the following sequence: ETDEEPEEPGRRGSFVEMVDNLRG... (SEQ ID NO: 55). This corresponds to amino acids 46--69 of the ORF-derived putative sequence. Based on this observation and others described below, the N-terminus of an active, naturally occurring, predominant human brain form of the enzyme is amino acid 46, with respect to SEQ ID NO: 2. Further processing of the purified protein provided the sequence of an internal peptide: IGFAVSACHVHDEFR (SEQ ID NO: 56), which is amino terminal to the putative transmembrane domain, as defined by the ORF. These peptides were used to validate and provide reading frame information for the isolated clones described elsewhere in this application.